PEDIATRIC CARDIOLOGY

An Association of Human Congenital Cardiac Malformations and Drinking Water Contaminants

STANLEY J. GOLDBERG, MD, FACC, MICHAEL D. LEBOWITZ, PhD, ELLEN J. GRAVER, MS, SUSAN HICKS, BS

Tucson, Arizona

During an informal study in 1973 it was noted that approximately one third of patients with congenital heart disease lived in a small area in the Tucson Valley. In 1981 groundwater for a nearly identical area was found to be contaminated with trichloroethylene and to a lesser extent with dichloroethylene and chromium. Contamination probably began during the 1950s. Affected wells were closed after discovery of contamination. This sequence of events allowed investigation of the prevalence of congenital heart disease in children whose parents were exposed to the contaminated water area as compared with children whose parents were never exposed to the contaminated water area. The contaminated water area contained 8.8% of the Tucson Valley population and 4.5% of the labor force.

Using their case registry, the authors interviewed parents of 707 children with congenital heart disease who, between 1969 and 1987, 1) conceived their child in the Tucson Valley, and 2) spent the month before the first trimester and the first trimester of the case pregnancy in the Tucson Valley. Two random dialing surveys showed that only 10.5% of the Tucson Valley population had ever had work or residence contact, or both, with the contaminated water area, whereas 35% of parents of children with congenital heart disease had had such contact ($p < 0.005$).

The prevalence of congenital cardiac disease (excluding syndromes, children with atrial tachycardia or premature infants with patent ductus arteriosus) in the Tucson Valley was 0.7% of live births and with syndromes was calculated to be 0.82%. The odds ratio for congenital heart disease for children of parents with contaminated water area contact during the period of active contamination was three times that for those without contact ($p < 0.005$) and decreased to near unity for new arrivals in the contaminated water area after well closure. The proportion of infants with congenital heart disease as compared with the number of live births was significantly higher for resident mothers in the contaminated water area than for mothers with no exposure. No other environmental agent could be identified that was localized to the contaminated water area, but one could have been missed.

The data show a significant association but not a cause and effect relation between parental exposure to the contaminated water area and an increased proportion of congenital heart disease among live births as compared with the proportion of congenital heart disease among live births for parents without contaminated water area contact.

(J Am Coll Cardiol 1990;16:155–64)

The present investigation originated from an informal study in 1973 that evaluated the addresses of children with congenital heart disease. Results suggested that approximately one third of these children came from a small area in the southwestern part of the city of Tucson, Arizona. In 1981, most of this identified area was noted to be similar to one in which drinking water was found to be contaminated by industrial chemicals. The water supply for the entire Tucson Valley is derived exclusively from groundwater. Aquifers approximately 4.3 miles (6.9 km) long and 3,000 to 4,000 feet (900 to 1,200 m) wide became contaminated with trichloroethylene in excess of the action standard of 5 ppb and to a lesser extent with dichloroethylene and chromium (1). Trace levels (well below action levels) of benzene, xylene and chloroform were also found in very localized industrial areas (1).

The contaminated water area occupied <5% of the area of the Tucson Valley. Contaminants had been placed on the ground surface or in unlined earthen holding pits, allowing percolation into groundwater (2) and evaporation into air.

From the Departments of Pediatrics (Cardiology) and Medicine (Epidemiology), University of Arizona, Tucson, Arizona. This study was supported by a grant from the Arizona Disease Control Research Commission, Phoenix, Arizona.

Manuscript received June 5, 1989; revised manuscript received December 26, 1989, accepted February 22, 1990.

Address for reprints: Stanley J. Goldberg, MD, Department of Pediatrics, University of Arizona Health Sciences Center, Tucson, Arizona 85724.

0735-1097/90/$3.50

Contaminated water was distributed to an industrial and residential area of the city from approximately the 1950s until 1981. Chromium levels were measured during the 1950s and thereafter; levels approached but did not exceed the action level (1). Trichloroethylene levels were initially measured in 1981; results exceeded guidelines in nine public wells (concentrations in these ranged from 6 to 239 ppb) (1,3). Dichloroethylene levels were usually between 5% and 10% of the trichloroethylene level (1,3). Concentrations of contaminants in excess of these levels were found in some private wells (3). Contaminated public wells were closed mainly during 1981.

Trichloroethylene is an organic solvent that can be absorbed orally or transcutaneously (4,5); in sufficient doses, it produces acute central nervous system, cardiac and hepatic toxicity (6). Trichloroethylene has also been studied (7) for carcinogenic activity in humans, but results were insignificant. Animal studies of teratogenicity have produced conflicting results. In small mammals, trichloroethylene inhalation has usually resulted in no observed teratogenesis (8–10), but studies of chick embryos have demonstrated significant general and cardiac teratogenesis, particularly if trichloroethylene was introduced early in gestation (11–13). Dichloroethylene has not been considered a teratogen (14,15).

The present investigation was designed to test the hypothesis that the proportion of offspring with congenital heart disease is greater for parents who had contact with the contaminated water area before and through the end of the first trimester of pregnancy than for parents who never had contact with the contaminated water area. The geography and medical referral pattern of Tucson provided a unique opportunity to study this problem. The geographic isolation of Tucson makes it unlikely that a child would be referred to another city for cardiac care. Almost all children with congenital heart disease are referred to the University of Arizona pediatric cardiology group or to one private practice pediatric cardiologist. Accordingly, it seemed probable that most parents who had a child with congenital heart disease could be identified through our registry and, thus, a registry-based case control study could be performed to test the hypothesis. Furthermore, comparison cases could be obtained by interviewing parents of patients with congenital cardiac disease who had never been exposed to the contaminated water area. Other control subjects could be obtained using routine survey methods.

Methods

Determination of limits of the contaminated water area. In 1973, an area was recognized (Fig. 1) that contained approximately one third of all patients with congenital cardiac disease in the Tucson Valley. Initial recognition was based on the fact that this group had 1 of 2 postal zip codes compared with 21 zip codes for the entire Valley. Figure 1

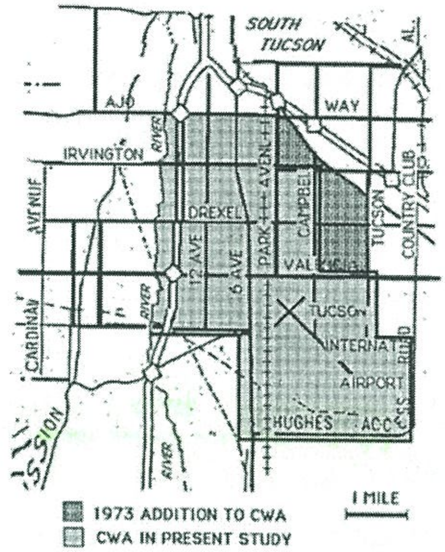

Figure 1. Local map of the contaminated water area (CWA). The contaminated water area utilized in this investigation is shown in the **light shaded area.** The area utilized to make the 1973 observation included all **shaded areas.** The **darker shaded area,** which was minimally populated during the period of contamination except for the most southwest portion, was excluded from the present study to more closely align with federal census tracts. The portion south of Valencia and east of the railroad tracks (shown as a **hatched vertical line**) was solely industrial and contained no residential population.

also shows the correspondence between the 1973 and 1981 area selected as the contaminated water area. For purposes of the present study, the 1973 area was modified slightly to better conform to established census tracts. In the area of interest, groundwater flowed generally from south to north. Accordingly, contamination decreased down gradient from the source as a result of dilution with noncontaminated water (1); because of dilution, precise contamination boundaries were impossible to delineate. Western and southern boundaries were easily defined because they were, respectively, a predominantly uninhabited riverbank and uninhabited desert. At the time of contamination, the eastern boundary was sparsely populated; minor boundary selection differences would, therefore, have little impact. The northern boundary was defined as 1 mile (1.6 km) north of the northernmost contaminated well. The contaminated water area thus defined consisted principally of residential areas, some businesses and one nonresidential industrial area containing the airport and related industry, electronic manufacturing, defense industry and other small manufacturing plants. A few retail businesses and minimal light industry were located along several major streets in the contaminated water area. The residential area, composed mainly of well tended single family homes and occasional apartment buildings, lies north and west of the industrial area and occupies part or all of seven census tracts. Determinations based on census tracts were necessary because most federal and state demographic data are available by census tract. If the area of interest occupied only part of a census tract, the percent of the population within the included area was based on relative area because population density was roughly uniform. This method induced minor errors in calculations, but block data (the alternative) would also induce error because population growth in the area was alinear between the 1970 and 1980 census and no interim data were available.

Study cases. The initial objective was to identify all children born in the Tucson Valley between January 1, 1969 and December 31, 1987 who were considered to have congenital heart disease by pediatric cardiologic evaluation. Cardiologists' records of all active, inactive and deceased patients were methodically reviewed to determine those patients who appeared to qualify for the study. The initial selection process excluded any patient whose records indicated that the parents had never lived in Tucson before or during the case pregnancy. The purpose of the secondary review process was to determine if remaining patients had a verified diagnosis of congenital heart disease established by cardiac catheterization, operation, autopsy, ultrasound study or, in a few cases, physical examination alone (the latter was reserved for a small number of children with ventricular septal defect seen early in the study). Excluded in the secondary selection were patients with recognized syndromes associated with cardiac abnormalities, children with supraventricular tachycardias or isolated ectopic cardiac beats without gross anatomic cardiac lesions, premature infants with patent ductus arteriosus, newborn infants with peripheral pulmonary stenosis and patients with a bicuspid aortic valve without stenosis or regurgitation. Parents of patients meeting secondary selection criteria were sought for personal interview. If a current contact address was not available, it was sought from registration records, the referring physician, local hospitals, clinics, public health authorities, the school system and contacts and visits with relatives, neighbors and places of work.

Data collection. Once personal contact was made with a family, verbal consent for obtaining answers to a questionnaire was obtained from the parent. A detailed address history formed the majority of the interview and focused on exact residence and work locations of both parents during the first trimester of pregnancy with the affected child, and then backward in time. Only parents who lived in the Tucson Valley for 1 month before and during the first trimester of the affected pregnancy were included. Additional questionnaire data included: 1) family history of congenital heart disease; 2) birth weight of index child; 3) parents' ages; 4) highest parental educational level; 5) occupation and occupational exposure to solvents; 6) ethnicity; and 7) history of rubella during pregnancy. The latter disqualified participation.

Table 1. Factors Controlled by Control Groups

Control group 1
Percent of population who had contact with the CWA
Control group 2
Percent of population who had contact with the CWA
Education of parents
Ethnicity by census tract
Occupation of parents
Control group 3 (case comparison group)
Percent of families with additional CHD
Type (severity) of CHD
Federal census
Ethnicity by census tract
City and census tract population information

CHD = congenital heart disease; CWA = contaminated water area.

Control cases (Table 1). Control group 1 was constructed by determining all telephone prefixes in the Tucson Valley and using random digit dialing of the four subsequent digits. Five hundred numbers were selected whose prefixes were in proportion to those assigned telephone numbers in the Tucson Valley. This group provided approximately equal sampling of persons living throughout the Tucson Valley. A minimum of four calls was made to each selected telephone number. If contact was established and consent to participate in the portion of the study received, the answering individual was asked if he or she or any member of the immediate family had ever lived or worked in the southwestern part of the city. Those who responded positively were asked for specific addresses.

Control group 2 was designed to be more specific than equal sampling of the entire Tucson Valley and was formed by developing 1,000 randomly assigned telephone numbers that proportionately mirrored the currently assigned prefixes of the population with congenital heart disease. If contact was established and willingness to participate was indicated by the answering individual, interviewers asked demographic information and historical questions about the location of work and residence of all related household members. Addresses for control subjects and case patients were converted to census tract data for comparison with federal and state demographic data. Interviewer bias was reduced because the interviewer did not know the boundaries of the contaminated water area.

Control group 3 was composed of children with congenital heart disease who fit the same criteria as used for case children except that control group 3 parents had no work or residence contact with the contaminated water area before or during the first trimester of pregnancy with the child who had congenital heart disease.

Live birth, fetal death, employment and population data. Live birth and fetal death data by census tract and year were obtained from the Arizona Department of Health Services Vital Statistics. Employment data for the contaminated

JACC Vol. 16, No. 1
July 1990:155–64

Table 2. Patient Diagnoses

Patient Diagnoses	CWA Cases*	Case Controls†
Anomalous pulmonary venous return	2	4
Aortic valve stenosis	14	24
Atrial septal defect	18	36
Atrial septal defect + OL	9	22
Cardiomyopathy	1	3
Coarctation of the aorta	10	17
Coarctation of the aorta + OL	3	12
Dextrocardia with minor lesions	1	2
Double outlet right ventricle	1	1
Double aortic arch	1	0
Endocardial cushion defect	1	0
Hypoplastic left heart	0	5
Hypoplastic right heart	0	1
Ebstein's anomaly	1	1
IHSS	1	0
Interrupted aortic arch	1	0
Mitral regurgitation	5	14
Mitral stenosis	1	2
Pulmonary atresia	3	4
Pulmonary artery hypoplasia	4	2
Patent ductus arteriosus	8	7
Patent ductus arteriosus + OL	4	3
Pulmonary valve stenosis	27	43
Pulmonary valve stenosis + OL	3	14
Subaortic stenosing ring	0	3
Taussig-Bing	0	1
Tricuspid atresia	2	2
Transposition of great vessels	8	13
Tetralogy of Fallot	5	12
Univentricular heart	0	2
Truncus arteriosus	2	1
Ventricular septal defect	95	161
Ventricular septal defect + OL	15	31
Other	0	18‡
Total	246	461

*Numbers of case patients with each diagnosis; †numbers of case controls (control group 3) with each diagnosis. Categories were created for the contaminated water area (CWA) cases and matched to case controls; ‡includes 18 cases for the case controls and none for the contaminated water area cases and consists of paired lesions in which a dominant lesion is not apparent (rather than listing individual diagnoses, this category was included to shorten the table). IHSS = idiopathic hypertrophic subaortic stenosis; OL = other lesions in addition to the primary lesion.

water area and Tucson Valley were obtained from a variety of sources including local and industrial publications (16,17) and government sources including the federal census (18–21).

Cardiac diagnoses and classification (Tables 2 and 3). Because some congenital cardiac lesions close spontaneously, the diagnosis closest to birth was recorded. Care was taken not to confuse patent foramen ovale with a true secundum defect, and patent ductus arteriosus in full-term infants was not included if it closed spontaneously within the first 2 months of life. Lesions were further classified by embryologic origin according to the method of Clark (22).

Results

Characterization of the contaminated water area. As we defined it, the contaminated water area consisted of 13.6 square miles (34.8 km^2) and contained 9.9% of the Tucson Valley population in 1970 (19) and 8% in 1980 (20). The 1980 census data (20) showed no significant differences between residents of the contaminated water area and the area immediately surrounding the contaminated water area in the following categories: education (percent high school graduates), occupation (percent employed in professional careers), mean income and number of women between 20 and 44 years old (approximating childbearing years). More Hispanics lived in the contaminated water area than immediately outside the contaminated water area.

Populations studied (Table 4). A total of 1,362 patients were identified who appeared from initial information and listed criteria to be candidates for interview. Of this group, we were able to locate and interview 1,144 patients (84%). We were unable to contact 218 families. Investigation of all available records for these 218 families showed that their child was born in Tucson, the cardiac lesion qualified for inclusion and the child had no identified syndrome. Although we had considerable information about these 218 patients, some of whom we continue to follow up as foster children, we were unable to obtain first trimester addresses and occupational exposure histories from their biologic parents. Of the remaining 1,144 located families, 406 were disqualified because 1) the parents moved to Tucson after the mother's first trimester of pregnancy, 2) the child had a syndrome associated with cardiac disease, or 3) the cardiac lesion was not an eligible one. Thirty-one children with congenital heart disease were born in Tucson to families who lived elsewhere during the first trimester. Accordingly, the remaining 707 families (246 with contaminated water area exposure and 461 with no exposure) formed the basis for this report. For control groups 1 and 2, interviewers were able to contact 88% of families in each group.

Results showed that contaminated water area exposure occurred in a variety of ways and during different time periods. Either or both parents could have been exposed to the contaminated water area. Residential exposure, employment exposure or a combination of both was found. Furthermore, exposure to the contaminated water area could occur: 1) before but not during the case pregnancy; 2) immediately before and throughout the first trimester (the experimental case); 3) during only part of the first trimester; or 4) after the first trimester (3 and 4 disqualified the family). Parents who lived or worked in the area of interest during the period of active contamination were assumed to have been exposed to contaminated water through its consumption. Finally, expo-

Table 3. Lesion Classified by Embryologic Etiology

Group	No.	Cellular Death	Extracellular Matrix	Cardiac Hemodynamics	Cardiac Looping	Mesenchymal Cell Migration	Targeted Growth	Other
CWA, all with contact	246	0 (0%)	1 (<1%)	208 (85%)	1 (<1%)	18 (7%)	2 (1%)	16 (7%)
Case controls	461	1 (<1%)	2 (<1%)	394 (85%)	2 (<1%)	33 (7%)	5 (1%)	24 (5%)
CWA precontact (M+F)	143	0 (0%)	2 (1%)	125 (87%)	1 (1%)	11 (8%)	0 (0%)	4 (3%)
Mother resident 1st tri	74	0 (0%)	1 (1%)	63 (85%)	1 (1%)	6 (8%)	0 (0%)	3 (4%)
Mother res + work	89	0 (0%)	1 (1%)	79 (88%)	1 (1%)	6 (7%)	0 (0%)	3 (3%)

CWA, all with contact = all families who had contact with the contaminated water area during all time periods (case controls contain data for all families in control group 3; none of these had contact with the contaminated water area before or during pregnancy); CWA precontact (M+F) = the 143 families who had contact with the contaminated water area before closure of the wells (data are included if either the mother [M] or the father [F], or both, had contact); Mother resident 1st tri = the 74 mothers who before well closure were residents of the contaminated water area before or during the first trimester of pregnancy; Mother res + work = all mothers who had contaminated water area contact prior to and during the first 3 months of pregnancy, either as a resident or as a worker. Other = diagnoses that do not fall into any of the categories.

sure to the contaminated water area could occur during or after the period of active water contamination. Numeric occurrence data for each permutation for each family with contaminated water area contact are contained in Table 5.

Of 707 qualified families, 246 (35%) had contaminated water area exposure of one or both parents. The remaining 461 families had no parental contaminated water area exposure before the end of the first trimester of the case pregnancy. These 461 families of children with congenital heart disease who had no contaminated water area history formed control group 3, a case comparison group.

Comparison of contact with the contaminated water area by families of children with congenital cardiac disease and by the general Tucson Valley population. Control group 1 data indicated that 10% of households interviewed had at least one member exposed to the contaminated water area. Control group 2 data showed that 10.8% of households had at least one member exposed to the area. Of 707 families who had children with congenital heart disease, 35% (more than threefold as many, $p < 0.005$) had contact with the contaminated water area.

Table 4. Total Case Families

Classification of Case Families	Total No.	Before Well Closure	After Well Closure
Total selected for interview	1,362		
Disqualified*	406		
First trimester elsewhere; born in Tucson	31		
Born in Tucson, first trimester in Tucson	925	537	388
Unable to contact	218	172	46
Adopted children	12	5	7
No contact, other reasons	206	167	39
CWA exposure (cases)	246	143	103
No CWA exposure (case comparison group)	461	222	239

*Disqualification for 1) born before arrival in city; 2) syndrome lesion, or 3) nonqualified lesion. CWA = contaminated water area.

First trimester pregnancies by resident mothers during the period of active contamination (Table 5). Eighty-nine mothers of case children had first trimester contaminated water area exposure. Of these 89 mothers, 74 had exposure as the result of residential contact, 24 had exposure as the result of employment and 9 had combined exposure. Residential locations for the same family were frequently multiple. A test of differences in proportions was used to compare the prevalence of congenital heart disease in offspring of residentially exposed mothers (74 of 10,907 or 6.8 of 1,000 live births in the contaminated water area) and nonexposed case comparison group 3 families (220 of 83,590 or 2.64 of 1,000 live births). The difference in proportion was significant ($p < 0.001$) (95% confidence interval 1.14 to 4.14), showing a significantly greater proportion for resident mothers. Furthermore, if all noncontactable families with children born before well closure were assumed to have had no exposure, the addition of their numbers ($n = 172$) to the unexposed group would still result in a significantly higher ($p < 0.02$) proportion for contaminated water area resident mothers than for mothers unexposed to the contaminated water area (392 of 83,590 or 4.7 of 1,000 live births).

Was the first trimester residential contact by the mother of case children the only important exposure? Seventy-four case mothers were contaminated water area residents during the first trimester and 15 additional mothers had employment contact with the contaminated water area during the first trimester. Twenty case fathers whose spouses did not have contact with the contaminated water area worked ($n = 19$) or lived ($n = 2$) (one father both worked and lived) in the contaminated water area immediately before conception of the child. Thus 111 (77%) of the 142 families had at least one parent who had contaminated water area first trimester (conception for fathers) exposure before well closure. All of the remaining case parents (32 of 142) had contaminated water area exposure before conception, but were no longer working or living in the contaminated water area 1 month

JACC Vol. 16, No. 1
July 1990:155–64

Table 5. Number of Families Who Had Contact With the Contaminated Water Area (CWA) Under Different Circumstances

Before or during first trimester CWA contact during contamination	
Either parent	246
Contact via residence	208
Contact via work	108
Mother	
Contact via residence	179
Contact via work	56
Both	27
Father	
Contact via residence	141
Contact via work	70
Both	27
Both parents	
Contact via residence	127
Contact via work	18
Both	9
First trimester contact during contamination	
Families with contact	142
Mother	89
Contact via residence	74
Contact via work	24
Both	9
Father	94
Contact via residence	72
Contact via work	35
Both	13
Mother or father	143
Contact via residence	88
Contact via work	55
Both	20
Father but not mother	20
Contact by residence	2
Contact by work	19
Both	1
First contact with CWA after well closure	
Total families	18
Mother	10
Contact via residence	8
Contact via work	2
Both	0
Father	11
Contact via residence	7
Contact via work	7
Both	3
Mother + father	7
Contact via residence	7
Contact via work	0
Both	0

before conception. To determine if residential first trimester maternal contaminated water area exposure was the only important factor, the proportion of children with congenital cardiac disease to total contaminated water area births was compared for resident mothers and for a group that included fathers as well as mothers (for the latter group consisting of

Table 6. Ethnic Background

Group	% Caucasian (non-Hispanic)	% Hispanic	% Other
Control group 2	75	18	7
Control group 3	80	17	3
Mean federal census for Tucson	76	20	4
Total study population	65	30	5
CWA exposure before well closure	46	52	2
CWA resident group only	38	59	3
Mean federal census of CWA	35	61	5
All persons exposed to CWA	48	49	3

Control group 2 is composed of random telephone contacts and control group 3 is case controls. CWA = contaminated water area.

both fathers and mothers who had contaminated water area contact, this computation allowed contact by employment or residence, or both). To accomplish this computation for the latter group, it was necessary to adjust the contaminated water area exposed population (that is, to increase the population) by taking into account the average duration of residence in the contaminated water area (mean 11 years), average employment duration in the contaminated water area and number of births/1,000 population. For purposes of this computation, all noncontactable families with children born before well closure were assumed to have had no exposure and all individuals with contaminated water area contact were assumed to have remained within the population (that is, none were assumed to have moved from the city). Results showed no difference in congenital heart disease prevalence for the group that included contact by residence or work for either parents (123 of 14,964 live births) as compared with results for resident mothers only (74 of 10,907 live births). These data show that adding additional factors beyond first trimester maternal contaminated water area contact did not increase the risk significantly.

Ethnic considerations (Table 6). Control group 2 very closely mirrored the ethnic distribution found by the census. Conversely, case children had a significantly different distribution ($p < 0.001$) than control group 2, mainly because contaminated water area families were more likely to be Hispanic than were families in the general Tucson area or in control group 2. Further subdivision of contaminated water area cases showed that 59% were Hispanic. Federal census data, however, showed that the percent of Hispanics in the contaminated water area was 57% in 1970 (19) and 64% in 1980 (20). Accordingly, Hispanics in the contaminated water area with cardiac malformations (59%) were present in proportion to their representation in the population. In addition, the proportion of Hispanics in the population of children with heart disease without contaminated water area contact (20%) was essentially similar to their representation indicated in the federal census. These data show that ethnicity does not appear to be an etiologic factor for heart disease in this study.

Table 7. Parent Age and Education

	Case Parents	Case-Control Parents
Maternal age (yr)	26.4	28.6
Maternal ed (yr)	11.9	14.5*
Paternal age (yr)	26.3	28.6*
Paternal ed (yr)	12.7	14.7*

*$p < 0.01$. age = age at delivery of case child; ed = number of years of formal education.

Characteristics of case parents (Table 7). Parents with contaminated water area contact were less educated ($p < 0.01$) and fathers were significantly younger ($p < 0.01$) at the time the case patient was born compared with noncontaminated water area case-control parents. Occupations of contaminated water area case parents and noncontaminated water area case-control parents were generally similar except that the proportion of professional fathers was higher in the noncontaminated water area group (22% versus 9%). The proportion of blue collar workers (22% versus 9%) was higher in contaminated water area parents. Federal census information for people living in the contaminated water area census tracts showed that mean income was just below the median for the Tucson Valley. Income data for control groups are not available. The prevalence of additional immediate family members with congenital heart disease was 3%, but many parents were young and could later have additional children with congenital heart disease. No significant difference in familial incidence of congenital heart disease was found between contaminated water area parents and controls. Known industrial solvent contact (many types, specifics frequently unknown) was reported for 10 of 246 contaminated water area families and 15 of 461 noncontaminated water area families. The difference in proportion for industrial solvent contact is not significant.

For the 218 families who could not be contacted, 16% had addresses within the contaminated water area at a time close to birth of the child; on the basis of population, approximately 9% would be expected.

Characteristics of case children. Male/female ratio was 124:122. Outcome (status at time of inquiry) of subjects indicated that 82.5% were alive with congenital heart disease, 13% were alive and now diagnosed as normal (this latter group contained mainly those with spontaneous closure of ventricular septal defect), 4% died from congenital heart disease and 0.5% died from other causes. For these factors, no significant difference was found between contaminated water area cases and case comparison group 3.

Prevalence of congenital cardiac disease. Of the 136,048 infants born from 1969 through 1987 in the portion of the Tucson Valley included in this study, 956 had a congenital heart defect that qualified for this study. These 956 include all births of infants with congenital heart disease by residents of the Tucson Valley, including those born to mothers who did not spend their first trimester in this location. Computation is made in this manner for comparison with other reported prevalence rates (that is, incidence is indexed to births rather than first trimester pregnancies). This ratio represents a prevalence rate of 7.02/1,000 live births. Adding children with syndromes associated with cardiac disease would increase the prevalence to 8.22/1,000 live births.

Odds ratio for exposed versus nonexposed parents. Missing data for 218 subjects sought for interview makes it impossible to compute the exact odds ratio for families with and without contaminated water area exposure; however, it is possible to compute a relative odds ratio for these two populations. To make a relative odds ratio meaningful, the contaminated water area population had to be corrected for (that is, increased by) the number of persons who held jobs in the area, the difference in birth rate between areas, the change in population over time and the frequency of job and residence changes. When these adjustments were taken into account, the odds ratio of congenital heart disease for children of all families exposed to the contaminated water area was three times greater during the period of active water contamination.

Occurrence of congenital heart disease in the contaminated water area after well closure for previously unexposed individuals (Table 5). Eighteen children with congenital heart disease were born between January 1982 and December 1987 to parents who had either work or residential exposure to the contaminated water area for the first time after the wells were closed. To determine if this number was greater than that expected, we approximated the number of new arrivals in the area from historical data of mean duration of employment and residence in the area, area birth rate/1,000 population, population change (the latter was made easier by the special census performed in 1985) and historic prevalence of congenital heart disease in the noncontaminated Tucson area (4.9/1,000 live births). On the basis of these data, 16.4 children with congenital heart disease would be expected to be born over this time span to new arrivals and 18 were found. The difference is not significant.

Cardiac lesions. Table 2 lists the dominant cardiac lesion for case study and control group 3 children; additional defects are not listed independently. Table 3 lists the number of contaminated water area and control group 3 children according to the suspected cause of lesions (18). No significant difference was found for lesion type when case and case-control values were compared.

Incidence of fetal death. Fetal death rate per 1,000 live births was not significantly different when comparison was made between the contaminated water area and the noncontaminated water areas.

Discussion

The most important finding of this study was that the proportion of cases of congenital heart disease among live births was significantly greater for mothers who had first trimester residential exposure to the contaminated water area than for mothers whose first trimester exposure was limited to the uncontaminated portion of the Tucson Valley. This increased proportion was maintained even if all parents who could not be located were considered to have had no contaminated water area exposure. Furthermore, adding data to include paternal exposure and exposure of the mother by employment did not significantly elevate the risk over that found for maternal resident exposure alone. The difference in proportion could not be ascribed to ethnic, economic or other factors that we studied. In addition, for individuals newly arrived in the contaminated water area after closure of the contaminated wells, the proportion of infants born with congenital heart disease decreased to the level experienced by parents without contaminated water area contact.

Environmental agents and human cardiac teratogenesis. The possibility that an environmental agent could alter cardiac development was suggested by Rose et al. (23), who tested the hypothesis that cardiac malformations could be explained completely on a genetic basis. Their data caused this hypothesis to be rejected and the authors concluded that environmental factors were at least partially responsible. Ethanol (24), diphenylhydantoin (25) and other agents have been previously reported to alter cardiac development. The authors are aware of no previous reports that showed an association between environmental exposure to trichloroethylene and abnormalities of human cardiac development; however, a recent investigation (26) has shown a possible association between trichloroethane, a closely related chemical, and human congenital cardiac disease. In that study, as in this one, dichloroethylene was also found in relatively low levels. Other human evidence supporting our findings was the report (27) that worker solvent exposure is associated with an increased prevalence of congenital heart disease.

Incidence of congenital heart disease. The overall prevalence of congenital cardiac defects for residents of the Tucson Valley was found to be 7.02/1,000 live births, a prevalence consistent with data of previous reports (28–31). This prevalence excluded children with syndromes known to be associated with congenital heart disease and those with mitral valve prolapse, bicuspid aortic valve without stenosis or regurgitation, patent ductus arteriosus in the premature infant and atrial arrhythmias and isolated ectopic beats. Inclusion of syndrome patients would increase the computed prevalence to 8.22/1,000 live births. Other studies of prevalence included lesions not included in this study.

Trichloroethylene versus dichloroethylene and chromium. The water-borne route is suspected because the rate of congenital heart disease decreased for infants whose parents were new to the contaminated water area after the affected wells were closed. Although no causative agent was identified by this investigation, trichloroethylene or dichloroethylene with or without a cofactor remains a possibility. Trichloroethylene was the contaminant most elevated in the drinking water. Dichloroethylene, a breakdown product of trichloroethylene or a cocontaminant, was elevated to a lesser extent. Human observations (32,33) regarding trichloroethylene and other anesthetics suggested an increased prevalence of miscarriages, but these reports are inconclusive. Dichloroethylene was also a possible cofactor in the California report (26); however, dichloroethylene is not a known teratogen (14,15). A companion report (34) to the California trichloroethane study (26) showed that the spontaneous abortion rate was significantly higher in the area that had elevated trichloroethane water levels compared with the rate of a control area. However, the fetal death rate was not higher in our contaminated water area, but reporting may have been incomplete. The third contaminant was chromium. Chromium injected into hamsters (35) and mice (36) caused skeletal changes and edema. No mention was made of cardiac examination in these animal studies. Chromium was probably not a factor in the present study because 1) only about 1% is absorbed by the oral route (37), and 2) distributed water had values below the action level of 0.05 mg/liter in almost all instances. This action level, however, is not based on teratogenesis. No other factor, water-borne or otherwise, was identified, but one may have escaped our detection.

Trichloroethylene metabolism. Considerable information regarding trichloroethylene metabolism is available. Ingested trichloroethylene is almost completely absorbed by the gut and is metabolized in the liver to trichloroethylene-glucuronide, trichloroethanol, trichloroacetic acid, oxalic acid and 2-hydroxy-acetylethanolamine (38). Excretion of metabolites by the kidney is usually complete within 3 days (39). Metabolites have been shown to cross the placenta readily into the fetal circulation and amniotic fluid (40–43). Furthermore, Land et al. (44) demonstrated that trichloroethylene exposure resulted in significantly increased numbers of abnormal spermatocytes in mice. Trichloroethylene has also been shown to concentrate in the ovary (45). Whether gonadal deposits are important in producing abnormal offspring is unknown. Studies of teratogenesis have produced mixed results. Three studies (8–10) of trichloroethylene inhalation by pregnant rats failed to show major teratogenesis. Two studies (11,12) on chick embryos, however, produced a different result. Bross et al. (12) injected very low dose trichloroethylene near the embryo and demonstrated that all experimental embryos but no control embryos had malformations. Elovaara et al. (11) injected trichloroethylene into the egg air space at 2 and 6 days and found no significant malformations. None of these studies reported cardiac abnormalities, but no study was designed in such a manner that detection of cardiac abnormalities would be a high probability. A recent study (46) of cardiac teratogenesis in chick embryos demonstrated that trichloroethylene infusion in doses of 5 to 25 μmol/egg, a dose similar to that used in other avian studies, was associated with three times ($p < 0.005$) as many cardiac defects as occurred for control solutions.

Possibilities regarding origin of cardiac teratogenesis. The present study elucidated neither the cause nor the mechanism for the observed increase in the proportion of congenital cardiac malformations. If trichloroethylene or dichloroethylene caused cardiac malformations, direct action on the fetus is one possibility. Exposure to the contaminated water area was almost always lengthy; the shortest was 4 months, but the mean was 11 years. Explanation of a delayed effect (exposure and conception separated by time), if this truly occurred, could have been due to deposition in the ovary (45) or creation of abnormal spermatozoa (44), or both. Furthermore, simultaneous ingestion of ethanol and trichloroethylene causes a significant increase in adverse effects because both alcohol and trichloroethylene compete for similar enzyme systems (47). The role of ethanol in this study is unknown. Further study of possible cardiac teratogenesis by these substances is warranted.

Individual dosage levels. It would be ideal to determine the contamination dosage that each contaminated water area parent received, but this is not possible because 1) parents both worked and lived in the contaminated water area or had multiple residences or work places; 2) the contamination level was measured only in 1981, but the period of study began 12 years earlier; and 3) the contamination level at a given water outlet was probably ever changing as the result of alterations in individual well flows, changes in area water usage and changes in water flow patterns. Accordingly, assignment of a single "dose" for each individual would be highly artificial.

Limitations of this study. This study has important limitations. 1) Although our findings suggest an association in the Tucson Valley between children born with congenital heart disease and parents having had exposure to the contaminated water area before or during the first trimester of pregnancy, the nature of this study does not allow establishment of a cause and effect relation between exposure of parents to water contaminants and congenital heart disease in their children. A cause and effect relation requires a separate experimental protocol. 2) The precise geographic area of water contamination in excess of Environmental Protection Agency guidelines is impossible to identify since the contaminated water area was served by wells that were contaminated in different time periods and to different extents. 3) Assurance cannot be offered that all patients were identified; we estimate that at least 95% were identified. Furthermore, we failed to contact 218 identified families. Our case identification process could have missed some children including any child referred to a cardiologist specializing in adult care who never came to the attention of a participating pediatric cardiologist; any child conceived in Tucson whose parents moved from the area before delivery and never reentered the Tucson medical care system; any child with unidentified congenital heart disease; and any child identified as having congenital heart disease but not referred (a poll of pediatricians practicing during the 1969 to 1981 period indicated that the latter was very unlikely). 4) Presented data allow no indication of the mechanism by which possible offending agent or agents caused the increased prevalence of congenital cardiac disease. Data of Loeber et al. (46), however, suggest that trichloroethylene is a cardiac teratogen in chicks. 5) Our study did not address noncardiac malformations. No systematic effort was made to identify all dysmorphic features of the patients with cardiac disease. 6) No dose-response curve could be established because doses were uncertain during much of the time and numerous parents had multiple exposures. 7) Address histories are based on recall, which over the span of numerous years could be faulty or biased. The same parent interviewed a second time did not always provide exactly the same previous address. Furthermore, the area has been "remodeled" by street construction in areas that previously were open desert with access dirt roads. Some parents were unable to precisely locate their prior housing amid the new streets. 8) Some difficulty was encountered with children with Hispanic surnames because it is common for these children to alternate between the mother's and father's surname. Dual inclusion of a child under different names was eliminated to the extent possible by birth date and lesion. 9) The model that we used to estimate new arrivals in the contaminated water area after well closure, although conservative and based on interview data, may contain inaccuracies.

We acknowledge the assistance of Alisa Plazonja (Tucson) for some of the interviews and Cheryl Czaplicki (Tucson) for editing. We thank Dr. Richard Brown (Tucson) for his cooperation with the study and Drs. Steven Englender (Phoenix), Glyn Caldwell (Phoenix) and Patricia Nolan (Tucson) of the State Department of Health Services and Pima County Health Department for their cooperation and considerable advice regarding the study and manuscript. Also appreciated is Dr. Herbert Abrams (Tucson) for his assistance.

References

1. Schmidt KD, Rampe JJ, Mock PA, Travers BC, Williams CK. Results of the Tucson Airport Area Remedial Investigation. Phoenix: Arizona Department of Health Services, 1985:1–123(plates 8 and 9, pages IX,XI,53–7,72–5).
2. Investigation of Subsurface Conditions in the Vicinity of Abandoned Waste Disposal Sites—Hughes Aircraft Company Manufacturing Facility, Phase II, Volume I, Tucson, Arizona. Tucson: Hargis & Montgomery, 1982:20.
3. Orloff KG. Health Assessment for Tucson International Airport Site. Tucson: Orloff, 1988:4.
4. Daniel JW. The metabolism of ^{36}Cl-labeled trichloroethylene and tetrachloroethylene in the rat. Biochem Pharmacol 1963;12:795–802.
5. Klaassen CD, Plaa GL. Relative effects of various chlorinated hydrocarbons on liver and kidney function in dogs. Toxicol Appl Pharmacol 1967;10:119–31.

6. Vignoli L, Jouglard P, Vignoli P, Terrasson de Fourgeres P. Acute intoxication by trichloroethylene ingestion. Med Leg Assicur 1970;18: 789-98.

7. Axelson O, Anderson K, Hogstedt C, Holmberg B, Molina G, Verdier A. A cohort study on TCE exposure and cancer mortality. J Occup Med 1978;20:194-6.

8. Dorfmueller MA, Henne SP, York RG, Bornschein RL, Manson JM. Evaluation of teratogenicity and behavioral toxicity with inhalation exposure of maternal rats to trichloroethylene. Toxicology 1979;14:153-66.

9. Healy TEJ, Poole TR, Hopper A. Rat fetal development and maternal exposure to trichloroethylene 100 p.p.m. Br J Anaesth 1982;54:337-41.

10. Schwetz BA, Leong BKJ, Gehring PG. The effect of maternally inhaled trichloroethylene, perchloroethylene, methylchloro-phorm and methyl chloride on embryonal and fetal development in mice and rats. Toxicol Appl Pharmacol 1975;32:84-96.

11. Elovaara E, Hemminki K, Vainio H. Effects of methylene chloride, trichloroethane, trichloroethylene, tetrachloro-ethylene and toluene on the development of chick embryos. Toxicology 1979;12:111-9.

12. Bross G, DiFrancisco D, Desmond ME. The effects of low dosages of trichloroethylene on chick development. Toxicology 1983;28:283-94.

13. Smith BE, Gaub ML, Lehrer SB. Teratogenic effects of diethyl ether in the chick embryo. In: Fink BR, ed. Toxicity of Anesthetics. Baltimore: Williams & Wilkins, 1968:269-77.

14. Murray FJ, Nitschke KD, Rampy LW, Schwetz BA. Embryotoxicity and fetotoxicity of inhaled or ingested vinylidene chloride in rats and rabbits. Toxicol Appl Pharmacol 1979;49:189-202.

15. John JA, Murray FJ, Smith FA, Schwetz BA. Teratologic evaluation of vinyl chloride, vinylidene chloride, and styrene in laboratory animals (abstr). Teratology 1978;17:48A.

16. Christman B. 200 Major employers of Southern Arizona. Tucson: Tucson Newspapers—Arizona Daily Star, 1986:2/24/87.

17. Metropolitan Tucson, Arizona Manufacturer's Directory. Tucson: The Tucson Economic Development Corp. 1984/1985:1-52.

18. US Bureau of the Census: Census of Population and Housing. Standard Metropolitan Statistical Area Census Tracts, Tucson, Arizona. Washington, DC: US Government Printing Office, 1960.

19. US Bureau of the Census: Census of Population and Housing. Standard Metropolitan Statistical Area Census Tracts, Tucson, Arizona. Washington, DC: US Government Printing Office, 1970.

20. US Bureau of the Census: Census of Population and Housing. Standard Metropolitan Statistical Area Census Tracts, Tucson, Arizona. Washington, DC: US Government Printing Office, 1980.

21. US Bureau of the Census: Census of Population and Housing. Standard Metropolitan Statistical Area Census Tracts, Tucson, Arizona. Washington, DC: US Government Printing Office, 1985.

22. Clark EB. Mechanisms in the pathogenesis of congenital heart defects. In: The Genetics of Cardiovascular Disease. Pierpont MEM, Moller JH, eds. Boston: Martinus-Nijhoff, 1986:3-11.

23. Rose V, Gold RJ, Lindsay G, Allen M. A possible increase in incidence of congenital heart defects among offspring of affected parents. J Am Coll Cardiol 1984;6:376-82.

24. Jones KL, Smith DW. The fetal alcohol syndrome. Teratology 1975;12: 1-10.

25. Monson RR, Rosenberg L, Hartz SC, Shapiro S, Heinonen OP, Slone P. Diphenylhydantoin and selected congenital malformations. N Engl J Med 1973;289:1049-52.

26. Swan S, Deane M, Harris J, Neutra R. Cardiac defects in relation to water contamination, 1981-1982, Santa Clara County, CA. In: Pregnancy Outcomes in Santa Clara County 1980-82: Reports of Two Epidemiological Studies. Berkeley, CA: Epidemiological Studies Section, California Department of Health Services, 1985:1-42.

27. Zieler S, Theodore M, Cohen A, Rothman KJ. Chemical quality of maternal drinking water and congenital cardiac disease. Int J Epidemiol 1988;17:589-94.

28. Richards MR, Merritt KK, Samuels MH, Langmann AG. Congenital malformations of the cardiovascular system in a series of 6,053 infants. Pediatrics 1955;15:12-32.

29. Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births: incidence and natural history. Circulation 1971;48:323-32.

30. Kerrebign KF. Incidence in infants and mortality from congenital malformations of the circulatory system. Acta Pediatr Scand 1966;55:316-20.

31. Carlgren LE. The incidence of congenital heart disease in children born in Gothenburg, 1941-1950. Br Heart J 1959;21:40-50.

32. Corbett TH. Anesthetics as a cause of abortion. Fertil Steril 1972;23: 866-9.

33. Corbett TH, Cornell RG, Endrres JL, Leiding K. Birth defects among children of nurse anesthetists. Anesthesiology 1974;41:341-4.

34. Swan S, Deane M, Harris J, Neutra R. Pregnancy outcomes in relation to water contamination, 1980-1981, San Jose CA. In: Ref 26:9.

35. Gale TF. The embryotoxic response to maternal chromium trioxide exposure in different strains of hamsters. Environ Res 1982;29:196-203.

36. Iijima S, Matsumota N, Lu CC. Transfer of chromic chloride to embryonic mouse and changes in the embryonic mouse neuroepithelium. Toxicology 1983;26:257-65.

37. Shamberger RJ. Beneficial effects of trace metals. In: Oehme FW, ed. Toxicity of Heavy Metal in the Environment. New York: Marcel Dekker, 1979:689-96.

38. Soucek B, Vlachova D. Excretion of TCE metabolites in human urine. Br J Ind Med 1960;17:60-4.

39. Nomiyama K. Estimation of trichloroethylene exposure by biological materials. Int Arch Arbeitsmed 1971;27:281-92.

40. Bernstine JB, Mayer AE. Passage of metabolites of chloral hydrate into amniotic fluid. Proc Soc Exp Med 1953;84:456-7.

41. Bernstine JB, Mayer AE, Hayman HB. Maternal and foetal blood estimation following the administration of chloral hydrate during labour. J Obstet Gynaecol 1954;61:683-5.

42. Beppu K. Transmission of the anesthetic agents through the placenta in painless delivery and their effects on newborn infants. Keio J Med 1968;17:81-107.

43. Helliwell PJ, Hutton AJ. TCE anesthesia: distribution in the fetal and maternal circulation of pregnant sheep and goats. Anaesthesiology 1950; 5:5-15.

44. Land PE, Owen EL, Linde HW. Mouse sperm morphology following exposure to anesthetics during early spermatogenesis (abstr). Anesthesiology 1979;51:S259.

45. Manson JM, Murphy M, Richdale N, Smith MK. Effects of oral exposure to trichloroethylene on female reproductive function. Toxicology 1984; 32:229-42.

46. Loeber CP, Hendrix MJC, Diez de Pinos S, Goldberg SJ. Trichloroethylene: a cardiac teratogen in developing chick embryos. Pediatr Res 1988;24:740-4.

47. Cornish HH, Adelfuin J. Ethanol potentiation of halogenated aliphatic solvent toxicity. Am Ind Hyg Assoc J 1966;27:57-61.